Articles

Association Between Facial Cutaneous Coccidioidomycosis and Meningitis

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The skin is frequently a site of extrapulmonary dissemination in patients with coccidioidomycosis. Clinical experience in an endemic area suggests an association between facial cutaneous coccidioidomycosis and meningitis. Awareness of this association is important because coccidioidal meningitis is the most ominous site of spread in coccidioidomycosis. In this study, we assess whether cutaneous dissemination involving the face is associated with meningitis to a greater degree than that limited to the body. We retrospectively reviewed the medical records of 201 patients from 1987 to 1996 with disseminated coccidioidomycosis and found 30 patients with cutaneous involvement. Their mean age was 29.5±11.6 years; 20 patients were male; 14 were African American, 12 were Hispanic, 3 were white, and 1 was Asian. Nineteen patients had facial involvement, and 11 had isolated body involvement. Meningitis developed in 11 patients, 10 with facial involvement and 1 with only body involvement. Patients with facial lesions were more likely to have meningitis (odds ratio, 11.1; 95% confidence interval, 1.1 to 529, *P*=.023). The identification of a subgroup of patients at significant risk of developing meningitis may allow earlier detection and perhaps improved management of patients with meningeal disease.

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Symptomatic infection with the pathogenic fungus *Coccidioides immitis* may present with a variety of clinical syndromes, but it usually manifests with self-limiting pulmonary symptoms.[1–6] Extrapulmonary dissemination occurs in about 5% of symptomatic cases,[7–9] leading to substantial morbidity and mortality.[1] The skin is a frequent site of extrapulmonary spread[6,10] and provides identifiable evidence of dissemination. The development of coccidioidal meningitis is an ominous event,[11,12] being fatal within two years if untreated.[3,13,14] In the medical literature, an association between cutaneous coccidioidal dissemination and coccidioidal meningitis has not been described. Our experience with coccidioidomycosis in the southern San Joaquin Valley of California has suggested an association between coccidioidal skin lesions, specifically facial lesions, and meningitis.

Before the 1991 to 1993 coccidioidomycosis epidemic in the Central Valley of California, the few patients with skin involvement made a study of this group difficult. During the epidemic, a growing number of patients with skin lesions allowed an analysis of the association between facial lesions and meningitis. In this study, we assess the frequency of meningitis in patients with facial skin lesions and compare these patients to those with body-only lesions. The identification of patients at a substantial risk of developing meningitis may allow early the detection and treatment of meningeal disease.

Patients and Methods

We did a retrospective medical record review of all patients (N = 201) in whom disseminated coccidioidomycosis developed from 1987 to 1996. Patients were observed at Kern Medical Center (n=184), Bakersfield, California, a 270-bed public hospital in the southern San Joaquin Valley, or in the practice of an infectious diseases specialist, RHJ, (n = 17). Of the 30 patients included in the study, 29 originated from Kern Medical Center. The study was approved by the Kern Medical Center Institutional Review Board.

The diagnosis of coccidioidomycosis was made if patients had a compatible symptomatic illness accompanied by positive results on a serologic test. The serologic

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TABLE 1.—*Demographics and Complement Fixation (CF) Titers of Patients With Cutaneous Coccidioidomycosis*

Variable	Group		
	Overall	Facial Involvement	Body Involvement
Number of patients	30	19	11
Sex			
Male	20	13	7
Female	10	6	4
Mean (±SD) age, yr	29.5 (±11.6)	30.4 (±12.4)	28.0 (±10.5)
Race			
African American	14	9	5
Asian American	1	—	1
White	3	1	2
Hispanic	12	9	3
Modal CF titer*	1:256	1:256	1:256

*Titers ranged from 1:2 to 1:512 for all groups.

test was performed by the Kern County Public Health Laboratory and was considered positive by the presence of any immunoglobulin M antibody, as detected by immunodiffusion assay or the presence of a complement fixation titer of 1:4 or greater. Coccidioidal meningitis was diagnosed by a characteristic clinical course, the identification of lymphocytic pleocytosis, and a positive complement fixation titer in the cerebrospinal fluid.

Skin involvement was defined as cutaneous coccidioidal infection demonstrated by culture or the presence of endosporulating spherules in pathologic specimens. *C immitis* was identified on specimens stained with Gomori's methenamine-silver stain of at least one lesion in all patients. None of the patients' skin lesions were solely immunologic manifestations of coccidioidomycosis (erythema nodosum or erythema multiforme).

Patients were categorized according to the location of their lesions: One group had facial involvement (only or with concomitant body involvement), and the second had only body involvement. Facial involvement was defined as any lesion on or above the mandible and body involvement as any lesion below the mandible. Lesions were described as plaques, nodules, ulcers, pustules, or verrucous eruptions. Patient demographics were described.

The association between meningitis and the location of cutaneous lesions was estimated with the odds ratio (calculated with the statistical software program Epi Info, Version 5 [Centers for Disease Control and Prevention, Atlanta, Georgia]), using the exact method for determining the confidence interval. The *P* associated with Fisher's exact test is given.

Results

Of the 201 patients with disseminated coccidioidomycosis who we observed, 30 (15%) were identified with coccidioidal skin involvement. Nineteen patients (63%) had facial involvement, and 11 (37%) had involvement of the body alone. Of the patients with facial involvement, 5 (26%) had facial involvement in isolation and 14 (74%) had concomitant body involvement. Patient characteristics are given in Table 1.

Meningitis developed in 11 (37%) of the patients with skin involvement (Table 2). Meningitis developed in 10 patients (53%) with facial involvement and 1 patient (9%) with body involvement (odds ratio, 11.1; 95% confidence interval, 1.1 to 529; *P*=.023). Of the patients with facial involvement and meningitis, 3 had facial involvement only, and 7 had face and body involvement.

Clinical Features

Seventeen patients presented with pulmonary symptoms, and skin lesions developed a mean (±standard deviation) of 2.8 (±2.9) months later. Eight patients presented with concurrent clinical symptoms and skin lesions. Five patients had no pulmonary symptoms or had uncertain histories. Of the 11 patients in whom meningitis developed, 6 had skin lesions before having meningitis (5 for 1 to 4 months, and 1 for 2 years); 3 had pulmonary disease for two to five months before meningitis developed; 1 had pulmonary disease for a month before skin lesions, and meningitis developed five months later; and in 1 patient, skin lesions developed two months after the patient had meningitis. Five patients had skin lesions develop during their pregnancy. Serologic tests were negative for the human immunodeficiency virus in the 23 patients in whom they were performed.

Chest radiographic findings were abnormal in 23 cases. A diffuse pulmonary process was the most common finding (11 patients [37%]), followed by hilar adenopathy (5 patients [17%]), lobar infiltrate (3 patients [10%]), pleural effusion (3 patients), and cavities (1 patient [3%]). Ten patients had bone involvement, and seven of these also had facial lesions. Two patients had evidence of joint disease, and two had prominent lymph node involvement. Four patients with meningitis had dissemination to additional sites.

Patients were observed for a mean of 40.4 (±26.1) months. The first patient included was first seen in 1987, and 20 were diagnosed during the epidemic (1991 to 1993). Nineteen patients are still being observed. Three patients died; all had facial involvement, and two had meningitis. Four patients had no further follow-up after symptoms resolved after a mean of 25.8 (±5.9) months. Three patients were unavailable for follow-up, and one was transferred to a different physician

Treatment

Of the 19 patients without meningitis, 12 received amphotericin B with fluconazole maintenance therapy. Four patients received fluconazole alone. Treatment of the 11 patients with meningitis included the administration of intravenous amphotericin B in 10 patients (6 also received amphotericin B intrathecally), and 1 patient was treated with fluconazole. As maintenance therapy, three patients with meningitis received amphotericin B

TABLE 2.—*Demographics and Clinical Features of Patients With Meningitis*

Patient	Lesion Location*	Sex	Race	Age, yr†	CF titer	CSF titer
1	Body	Female	Hispanic	17	1:256	1:1
2	Face and body	Female	Hispanic	24	1:128	1:64
3	Face and body	Female	African American	48	1:256	1:64
4	Face and body	Female	Hispanic	24	1:64	1:8
5	Face and body	Female	Hispanic	32	1:256	1:16
6	Face	Female	African American	20	1:8	1:16
7	Face	Male	African American	32	1:32	1:256
8	Face	Male	Hispanic	28	1:64	1:512
9	Face and body	Male	White	19	1:256	1:256
10	Face and body	Male	Hispanic	28	1:512	1:512
11	Face and body	Male	Hispanic	23	1:32	1:1

CF = complement fixation, CSF = cerebrospinal fluid

*Patients with lesions on their faces were 11.1 times more likely to have meningitis (95% confidence interval, 1.1 to 529, P=.023).
†Mean±standard deviation, 26.8 ± 8.6 years.

intrathecally, five received amphotericin B and fluconazole, and three received fluconazole alone.

Discussion

The epidemic of 1991 to 1993 highlighted *C immitis* as an extremely important pathogen.[6,15–18] Increased travel through endemic areas has caused cases of coccidioidomycosis to appear throughout the United States.[2,4,19] Increased morbidity and mortality are associated with more severe forms of pulmonary disease and with dissemination, particularly to the meninges.[11,12]

Our study allows clinicians to identify a subgroup of patients who may be at substantial risk of meningeal spread and is the largest study of patients with the cutaneous dissemination of coccidioidomycosis.

Patients with cutaneous dissemination represented 15% of the 201 patients with disseminated coccidioidomycosis observed during this time. Of our patients with skin involvement, meningitis developed in 11 (37%), which is similar to the traditional rate of 33% to 50% cited in the literature for any form of disseminated coccidioidomycosis.[10–12] Meningitis is not more or less likely to develop in patients with skin lesions compared to patients with other forms of dissemination. Patients with facial lesions were about 11 times more likely to have meningitis than patients with only body involvement. Of the patients with facial involvement, 10 (53%) had meningitis. Of the patients with only body involvement, meningitis developed in 1 (9%).

The reason for the association between facial cutaneous dissemination and meningitis is unclear. Perhaps patients with facial involvement have a higher concentration of organisms in a distribution that predisposes them to the development of meningeal involvement. *C immitis* reaches extrapulmonary locations such as the skin through hematogenous spread,[2,6] and drainage of these lesions into venous structures that articulate with the meninges is possible.

Some anomalies were noted in our study, including the overrepresentation of Hispanics with meningitis. Of the 12 Hispanics, 9 had facial lesions, and meningitis developed in 7 of them. In contrast, of the 14 African Americans, 9 had facial lesions, but meningitis developed in only 3. This may be an artifact of the patient base of Kern Medical Center or of the referral pattern. Meningitis developed in more women than men in our study, which differs from the male predominance noted in other coccidioidal meningitis studies.[11,12] The reason for this is unknown, but it may be attributed to our study that specifically examined patients with skin involvement. Of the patients examined, 5 (17%) had skin lesions during pregnancy.

With knowledge of this association, it becomes important to educate clinicians in the identification of skin lesions associated with coccidioidomycosis. Coccidioidal skin lesions do not have great specificity, and lesions such as papules and pustules are seen in many other skin conditions. Five of our patients had papular lesions or pustular lesions that could easily be overlooked, especially outside endemic areas.

Determining the clinical importance of facial skin lesions in a patient with coccidioidomycosis requires further study. Perhaps a patient with facial lesions should be treated proactively with a drug that crosses the blood-brain barrier and for a longer time than a person who has dissemination not involving such a high-risk area. Many factors such as age, sex, ethnicity, skin test reactivity, serologic test result, and response to therapy are important in deciding which therapeutic agent to give or the duration of treatment. As with any patient with disseminated disease, but more important in patients with facial skin involvement, a lumbar puncture is a mandatory part of the evaluation and can be helpful to a clinician in guiding therapy. A lumbar puncture may also be useful before the discontinuation of therapy.

Although this study is subject to the limitations of retrospective studies, it has clinical validity, and it is the

largest study of patients with cutaneous dissemination of coccidioidomycosis.

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